Neoadjuvant EGFR TKIs: toward personalized management in non-small-cell lung cancer

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Lung cancer remains the leading cause of cancer-specific death in men and women. Unfortunately, the majority of patients with non-small-cell lung cancer (NSCLC) have locally advanced or metastatic disease at diagnosis with a 5-year survival rate of only 4% (1). However, a minority of patients with NSCLC present at diagnosis with resectable disease. Treatment for early-stage disease in fit patients is focused on curative surgery, but 30% to 70% of patients with completely resected disease experience relapse (2,3), often by distant metastases, suggesting that early-stage NSCLC is frequently a micrometastatic disease at diagnosis (4,5) and adjuvant and/or neoadjuvany cisplatin-based chemotherapy are advised for patients with early-stage (6-8). Preoperative chemotherapy, also known as neoadjuvant or induction therapy, offers different potential advantages, including downstaging the tumor before surgery and thus increasing the chances of a complete resection (R0), as well as providing an opportunity to evaluate in-vivo effects of chemotherapy in resected specimens. Different randomized clinical trials evaluated the efficacy of neoadjuvant treatment in patients with earlier stage disease and although available data suggest a trend in survival benefit in favour of preoperative chemotherapy, the majority of individual trials have found no statistically significant differences (9). Furthermore, while adjuvant trials are able to generate biological samples before drug exposure (10), neoadjuvant regimens have the advantage of collecting tumour specimens after exposure to the agent under assessment.

Even though there are differents randomized phase III trial that evaluated the role of neoadjuvant chemotherapy in patients with early stage of NSCLC, at this time data from phase III trial that evaluated the role of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib are missing. Indeed the role of EGFR TKIs in early-stage NSCLC has not been established.

Data from different randomized clinical trials of first-line setting showed that higher response rates to EGFR TKI therapy have been observed in NSCLC patients who presented predictive factors like Asian ethnicity, never-smokers habit, female sex or present with adenocarcinoma histology. Among patients with adenocarcinoma, better response rate was also reported in tumors with lepidic growth pattern (bronchioloalveolar carcinoma or BAC). However, molecular studies have demonstrated that the presence of activating mutations in the tyrosine kinase domain of the EGFR gene, exons 19 and 21, are a better predictor of response to treatment with EGR TKIs (11).

The primary end-point for neoadjuvant treatment is response rate (ORR), and in previous study with EGFR TKIs in first-line setting, patients that harbouring EGFR mutations when treated with gefitinib or erlotinib showed an impressive ORR. Petrelli *et al*., reported the results of a meta-analysis of 13 randomized trials of patients with EGFR mutations that showed a median RR of about 63% in patients with EGFR mutations when treated with erlotinib or gefitinib (12). In addition to these results, Kris et al. reported a retrospective analysis on 1,006 patients with EGFR mutations in phase III randomized trials of gefitinib, that showed an ORR of about 70% in treatment-naïve e pre-treated patients, even if it is slightly lower in non-Asian trial (13).

In a recent issue of *Journal of Clinical Oncology*, Schaake *et al*. reported the results of an open-label phase II trial

of erlotinib as neoadjuvant treatment in patients with early-stage NSCLC (14). The study, conducted in four Netherlands hospitals, enrolled 60 patients with NSCLC (or highly probable NSCLC) eligible for surgical resection. Of the 60 patients, 29 fulfilled the criteria of the enriched populations (≥ two of the following features: female, adenocarcinoma, non-smoker, Asian), and the other 31 patients that did not meet these criteria (non-enriched population). All 60 patients received, before surgery, neoadjuvant erlotinib 150 mg daily for a course of 3 weeks and was stopped 72 hours before surgery. Tumor response was evaluated with CT-scans and FDG-PET/CT-scans after treatment with erlotinib, assessed following Response Evaluation Criteria in Solid Tumors (RECIST) measurement criteria, and metabolic response was assessed following the European Organisation or Research and Treatment of Cancer (EORTC) criteria for tumor response. Response rate (RR), evaluated by CT after 21 days of erlotinib treatment, was achieved in 3 (5%) of 60 patients, all in the enriched populations; instead metabolic partial response, measured by PET-scan, was seen in 16 (27%) of overall population, including 10 (34%) of 29 in the enriched population. Molecular analysis performed after surgery showed EGFR mutations in 7 of 56 patients (5 adenocarcinoma, 2 large-cell carcinoma) and KRAS mutations were found in 12 patients (9 adenocarcinoma, 2 large-cell carcinoma and 1 bronchioalveolar carcinoma). 4 patients harbouring an activating EGFR mutation had a metabolic response and necrosis more than 50% was seen in 3 of these patients. Survival results showed a 2-year PFS rate of 77% and OS of 82%; 10 patients died as a result of disease progression (median, 13 months; range, 5 to 24 months). Safety profile confirm data from registrative trial with erlotinib; skin rash and diarrhoea were common, though seven patients (12%) stopped erlotinib prematurely for unacceptable toxicity.

How should we interpret results from neoadjuvant trial by Schaake *et al.*, in the context of clinical practice? It seems that the outcome of patients included in this study are interesting, but it is needed to evaluated these results compared to other clinical trial of EGFR TKIs, although in different setting (treatment-naïve e pre-treated patients), inasmuch the role in early-stage NSCLC is not yet established. It is known, thant EGFR TKIs may provide a dramatic response in patients with NSCLC carrying EGFR activating mutations in the metastatic setting. In the IPASS study (15) (gefitinib *vs.* carboplatin-paclitaxel in pulmonary adenocarcinoma as first-line treatment), in the subgroup of 261 patients who were positive for the EGFR mutation, progression-free survival was significantly longer among those who received gefitinib than among those who received carboplatin-paclitaxel (P<0.001), and objective response rate was 71.2 *vs.* 47.3; and 43.0% *vs.* 32.2% (P<0.001) in overall study population treated with gefitinib compared to chemotherapy. In addiction to these data, Zhou *et al.*(16) reported the results from OPTIMAL phase III trial, comparing erlotinib to first-line chemotherapy (carboplatin-gemcitabine) in EGFR-mutations positive tumors, showed significantly prolonged progressive free survival (P<0.0001) and objective response rate (83% *vs.* 36%) with erlotinib, with a favourable toxicity profile. Results of these trials confirmed that treatment with EGFR TKIs is very effective in patients harbouring EGFR mutations, with an impressive PFS and ORR and showed a significant difference between EGFR mutations positive and negative populations. In fact, this is an important point of view to analyse the results' trial reported by S Schaake *et al.*

In the era of target therapy, different studies evaluated the role of prognostic and predictive impact of EGFR and K-ras mutations, and although there are a lot of trial that showed that these mutations are more likely to be found in never-smokers, Asians, females and tumors with adenocarcinoma histology, this does not mean that enriched population is a synonymous of EGFR mutated positive population, expecially in view that the major objective for neoadjuvant treatment is to improve objective response rate and prolong survival with the best treatment options available. In conclusion, although there is no phase III trial that evaluated the role of neoadjuvant EGFR TKIs, it is correct to think that this kind of treatment should be the best options for early-stage NSCLC harbouring an activating *EGFR* mutation, instead for patients without EGFR mutations that need a secure high objective response rate before surgery, at this time we can't consider EGFR TKIs as a valid treatment option as induction treatment

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